Antithrombin III concentrate to treat heparin resistance in patients undergoing cardiac surgery

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Objective: The purpose of this report is to describe the clinical use of antithrombin III concentrate in 53 patients who were found, in the operating room before cardiopulmonary bypass, to be heparin resistant.

Method: Resistance to heparin was determined to be present when greater than 600 U/kg body weight of heparin failed to prolong the kaolin-activated clotting time to more than 600 seconds in 53 aprotinin-treated patients. Blood samples were obtained for subsequent antithrombin III activity determination. Patients were then administered 500 U of antithrombin III concentrate, and the activated clotting time was remeasured. If the activated clotting time remained less than 600 seconds, a second 500-U dose was given.

Results: Of the 53 patients, 45 (85%) had subnormal measured antithrombin III activity, and the mean plasma antithrombin III activity level for the entire group was 67% (normal 80%-120%). Administration of antithrombin III concentrate (500 U in 45 patients and 1000 U in 8 patients) resulted in prolongation of the mean activated clotting time from 492 to 789 seconds without additional heparin. The mean heparin dose response increased from 36.5 to 69.3 $s \cdot U^{-1} \cdot mL^{-1}$ with antithrombin III treatment. Only one patient did not achieve the target activated clotting time, despite administration of greater than 600 U/kg heparin and 1000 U of antithrombin III concentrate, and was treated with fresh-frozen plasma.

Conclusions: On the basis of the criterion used in this report, most of the patients defined as being heparin resistant had subnormal plasma antithrombin III activity. Treatment with antithrombin III concentrate resulted in potentiation of the heparin effect to meet predetermined activated clotting time thresholds and allow for cardiopulmonary bypass.

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Clot formation during cardiopulmonary bypass (CPB) is prevented by the administration of heparin to catalyze the anticoagulant activity of endogenous antithrombin III (AT). In the operating room heparin-induced anticoagulation is most often monitored by the activated clotting time (ACT), and occasionally, patients undergoing heart surgery are identified as heparin resistant when large heparin doses fail to prolong the ACT to a level judged necessary for CPB.[1] This resistance to heparin, actually a state of an altered heparin dose response, is attributed to subnormal plasma AT activity, and heparin-resistant patients are often administered fresh-frozen plasma as a source of AT. Preparation of plasma, however, requires time for ordering, thawing, and delivery to the operating room and has a risk of viral transmission. Commercially prepared purified lyophilized human AT concentrates are available and may be stored in the operating room for immediate use. Levy and associates[2] reported that AT concentrate potentiated heparin responsiveness when added in vitro to blood drawn from patients with subnormal AT activity. Recently, Williams and associates[3] reported the administration of AT concentrate to 44 heparin-resistant patients and found it to compare favorably with results in a group of 41 similar

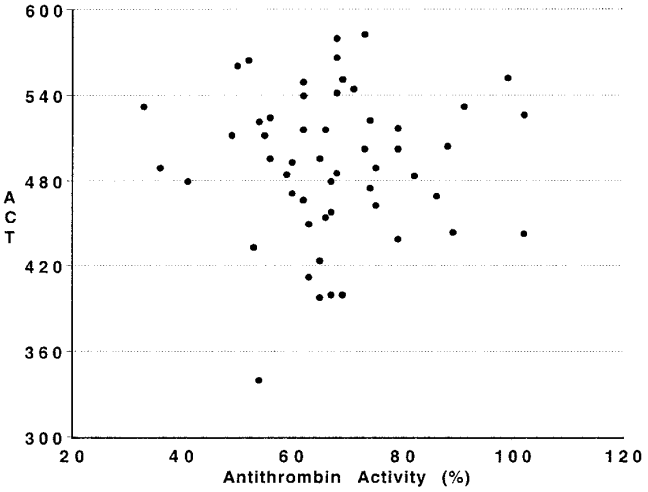

Figure 1. Scattergraph showing the apparent lack of correlation between kaolin ACT duration and AT activity after administration of greater than 600 U/kg heparin in 53 patients ($r = 0.01$).

patients who were treated with additional heparin. This report describes 53 patients who were found, at the time of surgical intervention, to have a diminished response to heparin and who were treated with AT concentrate. Before AT concentrate administration, blood was drawn from each patient for determination of AT activity.

Materials and Methods

The patients described in this report underwent operations during a 54-month period (November 1995 through May 2000). Fifty-three patients were identified as heparin resistant in the operating room before the institution of CPB on the basis of the failure of greater than 600 U/kg heparin to prolong the kaolin ACT to longer than 600 seconds. All 53 patients received aprotinin (38 with high-dose regimen and 15 with low-dose regimen) for various indications.[4] Initial heparinization was performed with the loading dose of 450 U/kg porcine heparin. ACT determinations were made with tubes containing the activator kaolin by using the Hemochron Model #801 (Technidyne Corp, Edison, NJ), according to the manufacturer's specifications. If the ACT was not sufficiently prolonged, then a second dose of heparin was administered so that the total dose of heparin exceeded 600 U/kg, and the ACT measurement was then repeated. If the ACT remained at less than the target level, blood was drawn from the patient for AT concentration determination. A single vial of AT concentrate (either Thrombate III, Bayer Corporation, Elkhart, Ind, or ATnativ, Pharmacia, Stockholm, Sweden) containing approximately 500 U of AT was administered through a central venous catheter over 3 to 5 minutes, and the ACT measurement was repeated. If the ACT was not sufficiently prolonged, a second vial of AT concentrate was administered.

Of the 53 patients, 24 (45%) were women; the average age was 71 years, and 21 (40%) were older than 75 years of age. Thirty-six of the 53 operations were urgent, 7 were emergencies, and 10 were elective. The following procedures were performed: coronary artery bypass (n = 37), valve replacement with or without coronary bypass (n = 14), and other (n = 2). The operation was a repeat sternotomy for 13 (25%) patients. Preoperative heparin exposure was present in 41 (77%) patients: continuous infusion in 38, heparin associated with dialysis in 2, and low-molecular-weight heparin in 1 patient. Eight (15%) patients had intra-aortic balloon pumps in place before the operations.

All operations were conducted with CPB. The pump prime solution contained 10,000 U of heparin. During bypass, the ACT was measured at 30-minute intervals. For these aprotinin-treated patients, a fixed-dose regimen was used, with heparin maintenance doses (100 U/kg) administered every 60 minutes of CPB, irrespective of ACT duration.[5] After separation from bypass, the initial protamine dose was 0.5 mg per 100 total heparin units.

The blood samples obtained for AT activity assay were drawn into tubes containing 3.2% trisodium citrate, centrifuged for separation of the plasma from the red cells and platelets, and then frozen. Assay of the plasma for AT activity was performed with colorimetric analysis (Stachrom; Diagnostica Stago, Parsippany, NJ). Results of the assay are expressed as percentages (range of normal activity, 80%-120%). Because the results of these determinations were not available until 24 to 48 hours after collection, they were not used to direct therapy.

Heparin dose-response relationships (HDRRs) were evaluated by using generated heparin dose-response slope values to facilitate the assessment of the potential effects of AT replacement on ACT responsiveness to heparin. Estimates of circulating whole-blood heparin concentration (WBHC) in units per milliliter were calculated by dividing the total heparin dose (in units) by the patient's blood volume (in milliliters). Increases in clot times after heparin administration (HDRR 1) or after AT concentrate administration (HDRR 2) were calculated by using baseline, postheparin, and post-AT concentrate ACT values and the following formulas, respectively:

HDRR 1 = Postheparin ACT – Baseline ACT/WBHC;

HDRR 2 = Postheparin ACT – Baseline ACT/WBHC.

These HDRR values were then compared with each by using a paired *t* test. The relationship between AT levels, WBHC values, and HDRR values was then assessed with multivariate linear regression statistical models.

Results

The mean per patient total heparin dose before AT concentrate administration was 49,745 U (642 U/kg), and the mean postheparin ACT duration was 492 seconds. The mean total heparin dose for the procedure was 71,032 U per patient, and the mean CPB time was 125 minutes. The mean plasma AT activity level of the 53 patients was 67%, and the median value was also 67% (range, 33%-102%; SD, 15%). Eight patients had serum AT levels greater than the lower limit of normal (80%), whereas 5 had severely subnormal levels (≤50%). The subgroup of patients with no preoperative heparin exposure (n = 12) had a mean AT activity level of 72% (range, 54%-102%).

Figure 1 shows each individual patient's ACT durations after the administration of greater than 600 U/kg heparin

TABLE 1. AT activity and ACT duration after treatment with 600 U/kg heparin or greater (mean dose, 642 U/kg)

	ACT <480 s	ACT 480-599 s
AT activity <80%	16/19 (84%)	29/34 (85%)
AT activity >80%	3/19 (16%)	5/34 (15%)

The incidence of subnormal AT activity (<80%) was nearly identical in the group of patients with an ACT of less than 480 seconds and the group of patients with an ACT of 480 to 599 seconds.

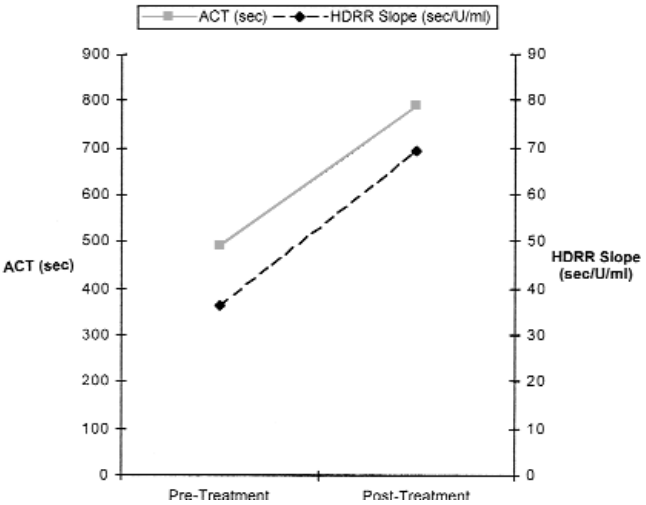

Figure 2. In 53 heparin-resistant patients the administration of AT concentrate (500 U in 45 patients and 1000 U in 8 patients) caused prolongation of the mean kaolin ACT from 492 to 798 seconds. This was associated with an increase in the slope of the HDRR value from 36.5 to 69.3 s·U^{-1}·mL^{-1}.

and the measured AT activity before treatment with AT concentrate. There appeared to be no correlation between the postheparin ACT and the magnitude of AT activity (r = 0.01). In the group of patients with ACT durations shorter than 480 seconds (a commonly used ACT threshold), 84% were AT deficient (16/19), which is nearly identical to the proportion of AT-deficient patients (85%) in the group with ACTs longer than 480 seconds (29/34, Table 1). After AT concentrate infusion (500 U in 45 patients and 1000 U in 8 patients) with no additional heparin, the mean ACT level rose from 492 to 789 seconds (Figure 2).

Eight patients required a second dose (approximately 500 U) of AT concentrate because of inadequate ACT prolongation after the first dose. The mean plasma AT level of these 8 patients was 74% (range, 56%-86%). Adequate ACT prolongation occurred in 7 of these patients after the second dose, and one required fresh-frozen plasma. Eight patients had normal AT activity determinations (mean, 92%; range, 82%-102%). Six of these patients achieved ACT durations of longer than 600 seconds after the initial 500-U dose of AT concentrate, and one received 1000 U to reach this ACT. One patient (whose pretreatment AT activity was 86%), despite treatment with 55,000 U of heparin and 1000 U of AT concentrate, required 2 U of plasma to raise the ACT from 470 to 673 seconds.

AT concentrate administration resulted in a greater response in ACT values, as demonstrated by statistically greater ($P < .0001$) HDRR values after AT concentrate (69.3 ± 29 s·U^{-1}·mL^{-1}) when compared with the values before administration of AT concentrate (36.5 ± 9.0 s·U^{-1}·mL^{-1}). In addition, AT levels ($P = .03$) and heparin concentration values ($P = .03$) were independently associated with ACT response to heparin (ie, HDRR values) before administration of AT concentrate. When assessing the factors associated with AT levels, only HDRR values before administration of AT concentrate were predictive ($P = .03$).

Discussion

Anticoagulation is maintained during CPB to prevent both catastrophic thrombosis and subclinical thrombin formation, which may contribute to intraoperative clotting factor consumption and postoperative coagulopathy. For satisfactory anticoagulation, sufficient levels of both endogenous AT and exogenously administered heparin are required. In vitro studies by Despotis and associates[6] suggest that the administration of AT to heparin-resistant patients may help to preserve the hemostatic system during CPB.

Acquired AT deficiency in patients undergoing cardiac surgery is associated with preoperative heparin treatment and intra-aortic balloon pump counterpulsation.[1-3,6] In this report 85% of the patients had been exposed to heparin shortly before surgical intervention. In our practice 29% of 1047 patients undergoing coronary artery bypass grafting surgery were treated with intravenous heparin just before surgical intervention in 1999 compared with 22% of our patients in 1989 and 1% in 1979. This reflects the increasingly urgent nature of contemporary cardiac surgery practice and the determination that heparin is an effective short-term therapy for acute coronary syndromes. As greater numbers of patients require preoperative heparin therapy and urgent surgical repair, it is expected that an increasing proportion of AT-deficient patients will be presenting for operations.

The patients in this report are a select group in that they all received prophylactic aprotinin, were found to be heparin resistant, had AT activity measurements, and were treated with AT concentrate. The aprotinin was administered before the withdrawal of blood for AT activity determination. Aprotinin administration does not, however, reduce plasma AT activity and is actually associated with increased AT activity during CPB.[7] Patients in this report were considered to be heparin resistant if the ACT remained

shorter than 600 seconds after the administration of 600 U/kg heparin. This ACT threshold is modestly (25%) longer than the kaolin ACT threshold (480 seconds) that is suggested as a minimum by aprotinin's manufacturer.[8] This heparin protocol is based on the observation that larger heparin doses reduce thrombin formation and clotting factor consumption during CPB more effectively than lower doses,[6,9] and when used with aprotinin, bleeding is reduced.[10] Although aprotinin does not affect the kaolin ACT to the extent to which it affects the celite ACT, at high aprotinin concentrations (400 KIU/mL), the kaolin ACT is, in fact, prolonged somewhat.[11] Furthermore, it has been demonstrated that the kaolin ACT response to heparin demonstrates a great deal of interpatient variability and that ACT values do not correlate well with plasma heparin activity during CPB.[12]

Various criteria have been used to define the state of heparin resistance. In 1994, Staples and colleagues[1] defined heparin resistance as a failure of 500 U/kg heparin to prolong the ACT (activator not specified) to 480 seconds. In 1995, Irani[13] reported the criterion of an ACT of 400 seconds after 300 U/kg heparin. More recently, Williams and associates[3] defined heparin resistance to be present when 450 U/kg heparin failed to prolong the celite-activated ACT to longer than 480 seconds in nonaprotinin-treated patients and longer than 600 seconds in aprotinin-treated patients. In effect, the definition used in the author's practice is quite similar to those reported by Staples and colleagues[1] and by Williams and coworkers.[3] Although the target ACT (600 seconds) is 25% longer than that required by Staples and colleagues or Williams and coworkers, the amount of heparin administered (600 U/kg) to achieve this goal ACT is also greater (20% more than Staples and colleagues and 33% more than Williams and coworkers). The definition of heparin resistance used in this series of patients successfully identified a group of patients with a high proportion (45/52 [85%]) of AT deficiency. In a similar fashion, Williams and colleagues[3] found 77% of their heparin-resistant patients to actually have subnormal AT activity. As shown in Table 1, 34 patients in this report had ACT durations of between 480 and 599 seconds after receiving more than 600 U/kg heparin. Of these, 29 (85%) had subnormal AT activity (mean AT activity for this group, 66%). Thus the heparin definition used in this report effectively identified patients for whom AT supplementation (either by plasma or AT concentrate administration) was likely indicated.

AT concentrate is a pooled human plasma product that has been subjected to fractionation procedures and heating to 60°C for not less than 10 hours to cause viral inactivation.[14] One vial (containing approximately 500 U of AT) is roughly equivalent to the transfusion of 2 U of fresh-frozen plasma, which has approximately 1 U of AT per milliliter. More specifically, AT activity is increased by approximately 1.4% for each unit of AT concentrate per kilogram of body weight.[15] The drug can be stored (refrigerated) in the operating room and be readily available for reconstitution and administration, thus eliminating the delay associated with ordering, thawing, and delivering fresh-frozen plasma from the blood bank. Williams and colleagues[3] compared AT concentrate to the administration of more heparin in patients who did not achieve predetermined celite ACT durations (see above) after initial treatment with 450 U/kg heparin. In that study AT concentrate (1000 U) was found to be more effective and faster for obtaining adequate anticoagulation than treatment with additional heparin. Likewise, in all but one of the 53 heparin-resistant patients of this report, AT concentrate treatment (either 500 or 1000 U) effectively prolonged the ACT, allowing for the institution of CPB without additional heparin or fresh-frozen plasma. This was associated with the near doubling of the heparin-ACT dose-response slope values that were observed after the administration of AT concentrate.

In this series of patients determined to be heparin resistant by means of ACT criteria, the majority had subnormal plasma AT activity, and the administration of AT concentrate increased the mean ACT by nearly 300 seconds. Although these findings demonstrate potentiation of heparin's effect, they do not lead to a claim of improved outcomes with AT concentrate administration compared with fresh-frozen plasma or compared with no treatment at all for patients who are found, intraoperatively, to be resistant to heparin. Nor do they prove the necessity for AT repletion, even for documented AT-deficient patients. It is known, however, that AT activity declines from baseline by about 50% during CPB, and thus very low levels would be expected to develop in patients with prebypass AT deficiency.[16]

The following may be concluded from this experience. First, failure of greater than 600 U/kg heparin to raise the kaolin-activated ACT to more than 600 seconds is associated with subnormal AT activity in the majority of patients. Thus heparin-resistant patients, on the basis of this definition, are very often AT deficient, although there did not appear to be a correlation between postheparin ACT duration and measured AT activity. Second, treatment of heparin-resistant patients with AT concentrate resulted in a significant increase in the ACT response to heparin with prolongation of the ACT to permit the institution of CPB.

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